FDA Briefing Document

Cellular, Tissue, and Gene Therapies Advisory Committee
and
Oncologic Drugs Advisory Committee Meeting

November 18, 2015

BLA 125593

Mycobacterium phlei Cell Wall-Nucleic Acid Complex

"MCNA"

Telesta Therapeutics

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the members of the advisory committee. The FDA background package often contains assessments, conclusions, and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the Mycobacterium phlei cell wall-nucleic acid complex Biologics License Application (BLA) with the Applicant's proposed indication to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AE	Adverse Event
AUA	American Urological Association
BCG	Bacillus Calmette-Guérin
BLA	Biologics License Application
CI	Confidence Interval
CIS	Carcinoma in situ
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
DFS	Disease-free Survival
DFS 1y	1-Year Disease-free Survival Rate
DNA	Deoxyribonucleic Acid
EAU	European Association of Urologists
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
EOS	End of Study
EOT	End of Treatment
F/U	Follow-up
FDA	Food and Drug Administration
IL	Interleukin
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention-To-Treat
Max	Maximum
Mb	Million Base Pairs
MBC	Metastatic Bladder Cancer
MCC	Mycobacterial cell wall-DNA complex
MCNA	*Mycobacterium Phlei* Cell Wall-nucleic Acid Complex
MCWE	Mycobacterium Cell Wall Extract
mDOR	Median Duration of Response
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-To-Treat
MOA	Mechanism of Action
N	Number of Subjects

N/A	Not Applicable
NCI	National Cancer Institute
ND	Not Done
NOD	Nucleotide-binding Oligomerization Domain
ODAC	Oncologic Drugs Advisory Committee
OS	Overall Survival
PAP	Papillary
PD	Progressive Disease
PI	Package Insert
PP	Per Protocol
QOL	Quality Of Life
RNA	Ribonucleic Nucleic Acid
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
T-E	Treatment-Emergent
TEAE	Treatment-emergent Adverse Event
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor
TNM	Tumor, Node, Metastasis
TTP	Time to Progression
TURBT	Transurethral Resection of the Bladder Tumor
ULN	Upper Limit of the Normal Range
US	United States
USPI	United States Product Insert
UTI	Urinary Tract Infection

1 Purpose of Advisory Committee Meeting

FDA convenes this joint advisory committee meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) and the Oncologic Drugs Advisory Committee (ODAC) to discuss the biologics license application (BLA) submitted by Telesta Therapeutics for Mycobacterium phlei cell wall-nucleic acid complex (MCNA) for the treatment of non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing.

In this BLA, the primary evidence of effectiveness comes from a single trial, EN3348-301 (Study 301). Study 301 was an open-label, multi-center study of the efficacy and safety of MCNA in the treatment of patients with NMIBC at high risk of progression and who were refractory to BCG. The primary efficacy objective was to demonstrate that a 1-year disease-free survival rate (DFS 1y) was not lower than 40% based on Kaplan-Meier estimate. The study population included subjects with different histologies: those with high-grade Ta and/or T1 papillary lesion(s) as well as those with carcinoma *in situ* (CIS) either alone or with papillary lesion(s) of any grade(s) (CIS-containing disease). However, the Applicant reported a DFS 1y of 25.0% in MCNA-treated subjects, so the study failed to achieve its primary endpoint. Using a responder landmark analysis, the FDA determined a DFS 1y of 20.9% (95% CI: 14.3% -29.0%), thus confirming the study did not reach its primary efficacy objective.

The safety data for MCNA also came primarily from Study 301. The most common MCNA-related treatment-emergent adverse events in Study 301 were dysuria, hematuria, fatigue, pollakiuria (daytime urinary frequency), and micturition urgency. The most common MCNA-related serious adverse events in Study 301 were urinary tract infection (UTI) and hematuria. Additional safety data were obtained from a Phase 3 Study, EN3348-303 (Study 303), which closed early due to poor patient accrual.

FDA review of this BLA identified the following major issues for consideration by this joint Advisory Committee:

- Single-arm trial design with a DFS endpoint which did not meet its stated objective;
- Estimation of the effect size of the primary endpoint of DFS 1y;
- Study population and indication statement;
- Concern that delaying cystectomy could contribute to the development of metastatic bladder cancer (MBC).

These issues could affect the interpretation of Study 301, particularly regarding whether the study results provide sufficient evidence of MCNA effectiveness in the intended patient population.

However, in light of the limited treatment options for patients with BCG-refractory NMIBC, FDA views the trial results, especially the results in the subpopulation of subjects with CIS-containing

disease, worth consideration in an advisory committee meeting. Please refer to Section 10 of this document for details.

2 Non-muscle Invasive Bladder Cancer

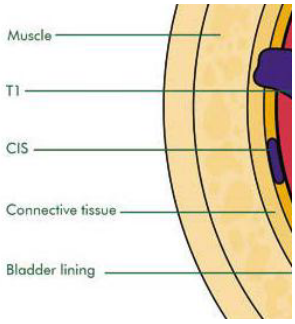
2.1 Bladder Cancer Overview

Bladder cancer is the most common malignancy of the urinary tract with an estimated 74,000 new cases and 16,000 deaths in the U.S. in 2015 [1]. Approximately 70-80% of new cases are superficial, involving only the inner bladder lining (urothelium) and submucosa. These superficial tumors are classified as non-muscle invasive bladder cancer (NMIBC).

Histology and Histologic Grade: The most common type of bladder cancer histology is urothelial (transitional cell) carcinoma in over 90% of tumors in adults [2].

The World Health Organization and the International Society of Urologic Pathologists have established a consensus classification system for malignant urothelial neoplasms in which urothelial cancer is classified as either low-grade or high-grade [3].

Figure 1. NMIBC Stages (Ta/T1/CIS)



Stage: NMIBCs are classified into three groups: Ta, T1, and CIS, based upon their growth pattern and depth of invasion.

- Ta tumors are noninvasive papillary (exophytic) lesions that are confined to the urothelium without penetration through the basement membrane
- T1 tumors are papillary lesions which penetrate through the basement membrane and extend into the underlying lamina propria ("connective tissue" on Figure 1).
- Carcinoma in situ (CIS) is a flat tumor, characterized by severe cellular dysplasia confined to the urothelium without discrete tumor formation. CIS may be associated with Ta or T1 papillary lesions or occur as an isolated growth.
- Higher T stages describe various degrees of muscle and perivesicular invasion.

Risk Stratification: To determine optimal treatment, NMIBC is stratified according to the risk of disease recurrence and progression to muscle-invasive disease. According to the 2013 European Association of Urologists (EAU) guidelines, the risk of progression is grouped into 3 strata, based on tumor grade, T stage, tumor size, and whether the tumor is recurrent or multifocal [4].

- Low risk: Ta, low grade, solitary lesion, < 3 cm (50% of patients)
- Intermediate risk: Multifocal, recurrent Ta or T1, low grade (35% of patients)

- High risk (15% of patients):
  - High-grade Ta or
  - High-grade T1 or
  - CIS: The presence of CIS without invasive urothelial cancer is associated with a high incidence of progression to invasive disease, even after transurethral resection and treatment with intravesical BCG [5].

Risk of Progression

The risk of progression to invasive disease varies from 45-50% for patients with high-grade Ta, T1, and CIS, and up to 90% for patients who are BCG non-responders at 6 months of treatment. Table 1 below shows the cumulative risk of disease progression to invasive bladder cancer and metastatic bladder cancer within 15 years of diagnosis for the high-risk histologies [6, 7].

Table 1. Risk of Disease Progression and Risk of Death from Metastatic Disease in NMIBC

High-grade NMIBC	Risk of disease progression	Death from metastatic disease
Papillary Ta	45%	n/a
Papillary T1	≥ 50%	35%
CIS	≥ 50%	20%
BCG Non-Responders at 6 months	≥ 90%	n/a

2.2 Treatment of Non-muscle Invasive Bladder Cancer

2.2.1 Initial treatment

The initial treatment procedure for NMIBC involves cystoscopy and complete transurethral resection of the bladder tumor (TURBT) whenever feasible. The goal of TURBT for papillary lesions is complete resection of all visible tumor(s). For CIS, complete surgical extirpation of the often diffuse tumor is not possible, thus biopsy is performed for diagnosis. TURBT for NMIBC provides a specimen for assessment of histology, grade, and stage. In addition, resection of all visible and resectable tumor(s) may improve local control of disease and bleeding symptoms.

For patients with papillary tumors with a low risk of recurrence after TURBT, a single dose of intravesical chemotherapy is often given [8].

For patients with intermediate or high-risk disease, a course of intravesical therapy is administered. The agent of choice is BCG, a live attenuated strain of *Mycobacterium bovis*, administered intravesically for treatment of CIS and prophylaxis to prevent bladder cancer recurrences following TURBT. Initiation of intravesical BCG is usually delayed for 2 – 3 weeks following TURBT to permit healing of the urothelium and decrease the risk of systemic side effects from BCG. It is thought that regular repeat exposure to BCG results in the optimal therapeutic effect; therefore, a vigorous schedule of weekly BCG induction, followed by regular BCG maintenance treatments, is recommended [9].

For all patients with stage T1 tumors (and select patients with CIS or Ta tumors in whom the original staging surgery was inadequate), a restaging TURBT is usually considered before intravesical immunotherapy with BCG is administered.

When administered intravesically, BCG promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and lymphocyte infiltration in the urothelium and lamina propria of the urinary bladder. The exact mechanism of action is unknown, but the anti-tumor effect appears to be T-lymphocyte-dependent [10]. For patients found to have muscle-invasive disease on the initial staging work-up, a cystectomy is typically indicated.

2.2.2 Treatment of recurrent disease

Despite therapeutic BCG (for CIS) and adjuvant BCG (for high-grade Ta or T1), disease recurrence occurs in up to 50% of patients [11]. Retreatment of recurrence with BCG depends on the features of the disease (stage and grade), time to relapse, and prior therapy. Patients who have late relapses of high-risk NMIBC after prior BCG may again be treated with repeat TURBT procedure (when indicated) and BCG, depending upon multiple clinical factors.

2.2.3 Treatment of refractory disease

Definition: A recent FDA-AUA (American Urological Association) workshop panel defined BCG-refractory disease as patients [with persistent disease] who received 2 induction courses of BCG, induction plus maintenance (usually within 6 months), or were intolerant of BCG [12].

Treatment: For patients who have tumors that are no longer responsive to BCG, therapeutic options are limited.

1. Cystectomy is recommended for patients at high risk for progression to muscle-invasive disease (defined as recurrence of high-risk disease within six months after initial TURBT or intravesicular therapy). The disease-specific survival of patients with BCG failure who undergo early cystectomy before progression to muscle invasion is 80 to 90%, at 5 years, and falls to 55% if the disease progresses to muscle invasion [6, 13, 14].

2. Valrubicin is the only FDA-approved drug for BCG-refractory CIS. In 90 study subjects with BCG-refractory CIS, 70% had received at least 2 courses of BCG and 30% had received one BCG course and at least one additional course of another intravesical agent. Sixteen subjects (18%) had a complete response documented by cystoscopy and biopsy at 6 months. Median duration of response from start of treatment varied according to the method of analysis (13.5 months if measured to last bladder biopsy without tumor and 21 months if measured until time of documented recurrence) [15].

Table 2. FDA-Approved Therapy for BCG-refractory carcinoma in situ (CIS)

FDA-Approved Product	Approval Year/ indication	Endpoint(s)	Clinical Benefit / Effect
Valstar (valrubicin)	1998 / BCG-refractory CIS	RR	6-month RR 18% mDOR 21 months measured from initiation of Valstar until documented recurrence

[Source: Valstar (USPI)]
Abbreviations in Table: mDOR, median duration of response; RR, response rate.

3. Other chemotherapeutic agents, such as doxorubicin, thiotepa, mitomycin, and gemcitabine, have been used in the setting of BCG-refractory disease but have limited activity and are considered investigational in this setting [6, 7, 16]. Thus, the standard of care for patients who have failed after optimal BCG treatment has been to proceed with cystectomy [8, 16].

3 Product Description

The investigational product, Mycobacterium phlei cell wall-nucleic acid complex (MCNA), is a sterile aqueous suspension containing mycobacterial cell wall fragments complexed with nucleic acid (DNA and RNA) oligomers. The biology of *Mycobacterium phlei*, origin of the strain, derivation of MCNA and its proposed mechanism of action are described in this section.

3.1 *Mycobacterium phlei*

Mycobacterium phlei is a rod-shaped, non-motile, non-spore forming, free-living mycobacterium that is widely distributed in soil and on plants. Although typically nonpathogenic, on rare occasions it has been found to cause nontuberculous infections in both immunocompromised and immunocompetent individuals [17].

M. phlei has mycolic acid in the cell wall and is categorized as a rapidly growing mycobacterium. It has the unique ability to grow at high temperatures, 52°C, and ferment carbohydrates like arabinose, mannitol and xylose [18]. *M. phlei* can also grow in the presence of a mycobacteria selective dye, Malachite green. *M. phlei* colonies appear wrinkled, rough, and deep yellow in color on standard mycobacteria selection/differentiation media such as Lowenstein-Jensen.

Although *M. phlei* has a relatively small genome of 5.64 million base pairs (Mb), it possesses one of the highest overall GC contents (70%) among mycobacteria [17].

3.2 Mycobacterium phlei cell wall-nucleic acid complex (MCNA)

The *M. phlei* strain used in the MCNA manufacturing was originally isolated in (b)(4) before 1964. Telesta obtained the strain in 1979 and created a *M. phlei* Master Seed from which all Telesta MCNA has been derived.

Several different product formulations were studied over the course of product development. These are briefly described in the table below. MCC Suspension and MCNA are quite similar in product quality attributes.

Table 3. Manufacturing and Formulation Summary for MCNA and Previous Formulations

Formulation	Method of *M. phlei* cell rupture	Excipients	Adjuvant(s)
MCWE	Uses both physical and chemical processes	(b)(4) Preservative	Mineral oil
MCC Emulsion	Same as MCWE	(b)(4)	Mineral oil
MCC Suspension	Uses a physical process that is different from MCWE	(b)(4)	none
MCNA Suspension	Same as MCC Suspension	Water for Injection	none

The MCNA Suspension is a sterile drug product. It is supplied in 10 ml clear glass vials, each containing a recoverable product volume of 8 ml. Prior to administration, 8 ml of the MCNA Sterile Suspension is aseptically mixed with 42 ml of sterile water for injection in a sterile syringe and slowly instilled into the bladder using a urethral catheter.

3.3 Proposed Mechanism of Action (MOA)

MCNA is proposed to exert its anti-cancer activity via both direct and indirect (immune-mediated) effects on the tumor cells. The BLA contains study reports and cites publications from *in vitro* and animal studies of *M. phlei* cell wall-nucleic acid complexes (including MCNA and the earlier formulation, MCC suspension) intended to support the proposed MOA. Direct contact with tumor cells can inhibit tumor cell proliferation, lead to cell-cycle arrest, and ultimately result in tumor cell death [19]. Multiple indirect, immune-meditated effects of MCNA on tumor cells are possible. Briefly, mycobacterial cell wall and nucleic acid components present in MCNA and MCC suspension are known ligands for pattern recognition receptors (PRRs) on mononuclear immune cells (i.e., dendritic cells and macrophages) [20]. The BLA contains data indicating that specific PRRs including Toll-Like Receptor (TLR)-2, Nucleotide-binding oligomerization domain-containing 2 protein (NOD)-2, and to a lesser extent TLR-3 and TLR-5, are activated by MCC suspension. *M. phlei* cell wall-nucleic acid complexes have also been shown to induce pro-inflammatory cytokines, including interleukin (IL)-12, IL-6, and Tumor Necrosis Factor (TNF)-α [21]. Such local cytokine release triggers additional immune cell activation to promote anti-tumor immune responses [22]. Removal of mycobacterial DNA from MCC suspension by DNase I treatment reduces its capacity to stimulate IL-12 production *in vitro*, although the presence of CpG methylated DNA is not required for this activity [21].

While the precise immunological mode of action of MCNA is unknown, it is likely to share many commonalities with BCG-mediated immunostimulation [22]. However, differences between MCNA (sterile aqueous suspension containing mycobacterial cell wall fragments complexed with nucleic acid oligomers) and BCG (live, attenuated mycobacterium) may result in some differences in MOA. No *in vitro* or animal studies were performed to compare the direct or indirect effects of MCNA and BCG on tumor cells, or how the effects of MCNA may be altered by, or dependent on, prior exposure to BCG.

FDA Comment: It should be noted that all subjects from Studies 301 and 303 received prior treatment with BCG, and these studies did not enroll any BCG-naïve subjects. Thus, it is unclear if the responses to MCNA treatment observed in these trials required prior treatment with BCG to prime the MCNA response.

4 MCNA Development Milestones

12/2/2005	Original IND submission by Bioniche (product formulation MCWE, then MCC)
2006–2012	Phase 2 trial Study 301 performed in BCG-refractory and recurrent population (product changed from MCC to MCNA)
10/4/2010	Phase 3 trial Study 303 submitted for BCG recurrent and refractory patients
11/5/2012	Study 303 terminated due to poor enrollment
12/05/2014	IND Sponsorship transferred to Telesta Therapeutics

06/30/2015 BLA submission

5 Study EN3348-301 ("Study 301")

The efficacy claim of MCNA is based on Study 301 described below, a single-arm, open-label trial conducted in the U.S. and Canada. The Applicant also conducted another randomized trial, Study 303 comparing MCNA with intravesical mitomycin. Study 303 was aborted early due to slow accrual and mitomycin shortage. Study 303 is further described in Section 8 of this document.

Study 301 Title: Open-label, multi-center study of the efficacy and safety of MCNA in the treatment of patients with non-muscle invasive (superficial) bladder cancer at high risk of progression and who are refractory to BCG

5.1 Objectives

Primary efficacy objective: To demonstrate that 1-year disease-free survival rate was not lower than 40% by Kaplan-Meier estimate. Disease-free status was defined as alive with no evidence of bladder cancer.

Secondary efficacy objectives: To determine the DFS rate at 3 months, 6 months, and 2 years; time to progression; overall survival

Primary safety objective: To determine the frequency of treatment delay or discontinuation due to adverse events (AEs)

Secondary safety objective: Descriptive evaluation of AEs

5.2 Major Eligibility Criteria

5.2.1 Inclusion Criteria

1. Males or females age ≥ 18 years.
2. NMIBC refractory to BCG
   a. Refractory was defined as evidence of persistent high-grade NMIBC after at least 6 months have elapsed following the start of a full induction course of BCG with or without maintenance/re-treatment at 3 months.
   b. Refractory was also defined as evidence of recurrent high-grade NMIBC within 2 years from the start of a full induction course of BCG and after achieving a disease-free status 6 months post-induction. The recurrent high-grade tumor must be evident within 6 months after receiving a dose of BCG.

3. High-grade Ta and/or T1 papillary lesion(s); Specimen must include a portion of the underlying muscle to confirm stage T1;
   or
   CIS, with or without papillary lesion(s) of any grade(s)
4. All visible papillary lesions must be resected by TURBT within 56 days prior to beginning of study treatment
5. Histologically confirmed diagnosis of high-grade disease must be within 56 days prior to beginning of treatment
6. Absence of urothelial carcinoma involving the upper urinary tract or prostatic urethra (confirmed by upper tract radiological imaging and/or biopsy) within 12 months from beginning of study treatment
7. ECOG 0, 1, or 2
8. Life expectancy > 5 years

FDA comment: Subjects who had papillary disease alone were rendered disease-free at baseline by surgical resection. Thus, in the absence of any identifiable disease, use of MCNA in these subjects was for adjuvant treatment. A single-arm trial without a concurrent control could not adequately evaluate DFS, a time-to-event endpoint, in these subjects. In contrast, CIS-containing disease rarely undergo spontaneous regression; therefore, in subjects who had CIS-containing disease at baseline, a disease-free status after MCNA treatment would likely reflect a treatment effect from MCNA. Use of MCNA in subjects with CIS-containing disease and resultant complete response may be interpretable and not subject to the uncertainty regarding the treatment effect estimation, as discussed in Section 10.2. However, results based on an analysis combining subjects who had resected papillary disease alone and subjects who had CIS-containing disease would be difficult to interpret.

5.2.2 Exclusion Criteria

Any of the following resulted in exclusion:

1. Current or previous history of muscle-invasive bladder tumor ($\geq$ T2)
2. Current or previous history of metastatic bladder cancer (either lymph node-positive disease or distant metastases)
3. Current systemic cancer therapy (cytotoxic, cytostatic, or immunotherapy)
4. Current or prior pelvic external beam radiotherapy
5. Current urinary tract infection (UTI)
6. History of malignancy of any organ system, treated or untreated, within the past 5 years (with the exception of adequately treated basal cell or squamous cell carcinoma of the skin, Stage T1 prostate cancer, cervical CIS)

5.2.3 Baseline Eligibility Determination

Stage and grade of tumors for study entry eligibility were to be determined by the pathologist at the local hospital/center where the patient received treatment (referred to as “local pathologist”).

The TURBT/biopsy eligibility material was also to be sent to a reference pathologist (referred to as "central pathologist") for review to confirm or disagree with the local pathologist's diagnosis.

FDA comments: Discrepancies between local and central pathology review could lead to uncertainty regarding the tumor histologies the subjects had at baseline, affecting the interpretation of the trial results (See 7.1.2 below).

5.3 Treatment and Study Drug Administration Schedule

The study was to be divided into 3 phases: Induction, Maintenance, and Follow-up (Figure 2).

The Induction Phase was to cover a period of 6 weeks, during which subjects would receive 6 weekly intravesical instillations of MCNA. The MCNA suspension was to be reconstituted such that each dose consisted of 8 mg MCNA in sterile water for a total instillate volume of 50 mL. All subjects were to receive the same dose for each intravesical instillation.

At Month 3, patients were to be evaluated for disease progression. Evaluations included standard cystoscopy examination and voided urine cytology. Subjects who were disease-free at Month 3 were to enter the Maintenance Phase of the study. Subjects with non-muscle invasive disease at Month 3 may, at the discretion of the investigator, receive either a second induction treatment of 6 weekly instillations or Maintenance treatment of 3 weekly instillations. Patients who progressed to T2 disease at Month 3 were to be discontinued from further study treatment.

The Maintenance Phase was to cover the period from Month 3 to Month 24. During this time, subjects were to receive weekly MCNA instillations for three weeks at Months 3, 6, 12, 18, and 24, and evaluations were to be performed every 3 months at Months 3, 6, 9, 12, 15, 18, 21 and 24. Evaluations were to include cystoscopy examination and urine cytology. Biopsies were to be performed for all evident or suspicious areas or when recurrence was suspected. At Month 6, mandatory biopsies were to be performed for all subjects.

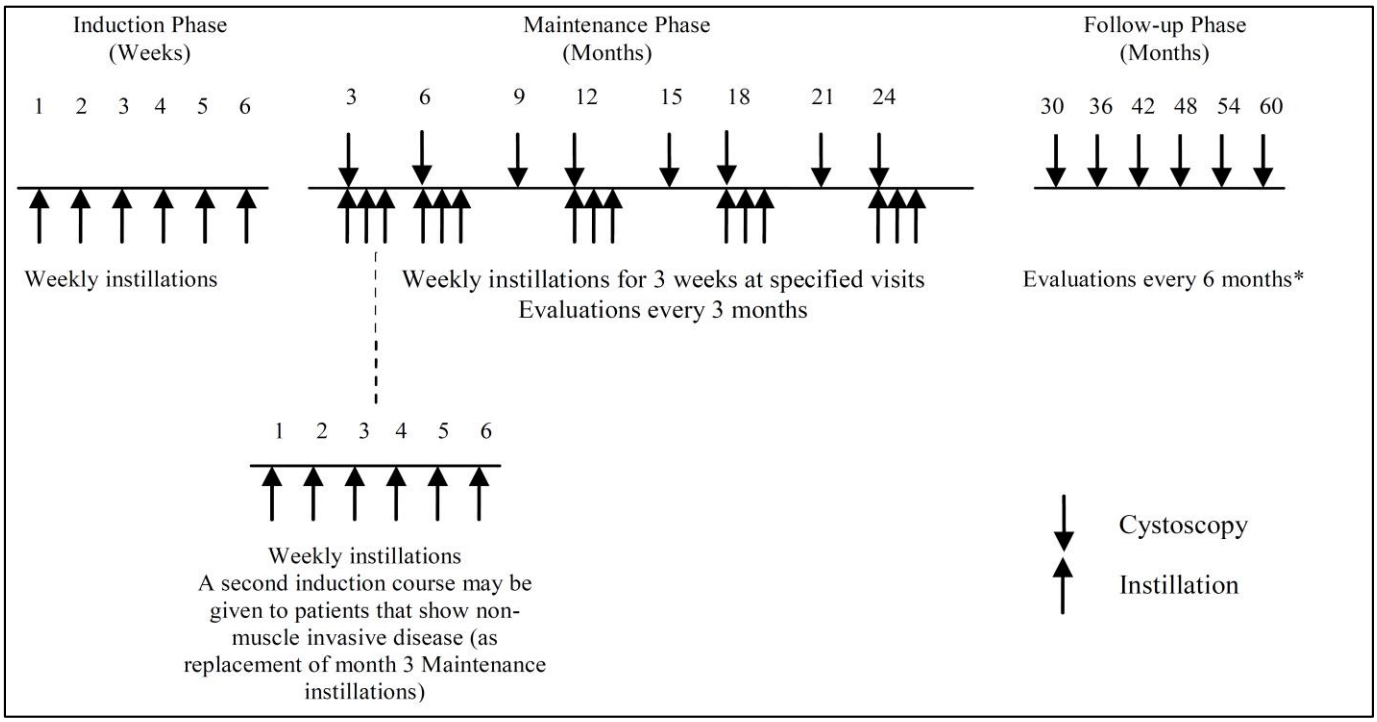
At Month 6 and thereafter at each evaluation visit, subjects were to be managed according to the following results:

- Subjects who were not disease-free were to be withdrawn from further study treatment and referred to other therapies at the discretion of the investigator. These subjects remained on study (off treatment) for follow-up of secondary endpoints such as overall survival, cystectomy, and the development of metastatic bladder cancer. However, subjects who developed only low-grade papillary tumors during the Maintenance Phase could continue to receive MCNA instillations at the discretion of the investigator, in consultation with the Applicant. However, these subjects with low-grade papillary tumors were to be considered as MCNA treatment failures (i.e., tumor recurrence).
- Subjects who were disease-free were to continue on maintenance treatment.

The Follow-up Phase was to extend after Month 24 up to Month 60. During this phase, evaluations were to be performed every 6 months, including cystoscopy, cytology, and biopsy when clinically indicated. The length of follow-up for individual subjects could vary, depending upon their time of enrollment into the study.

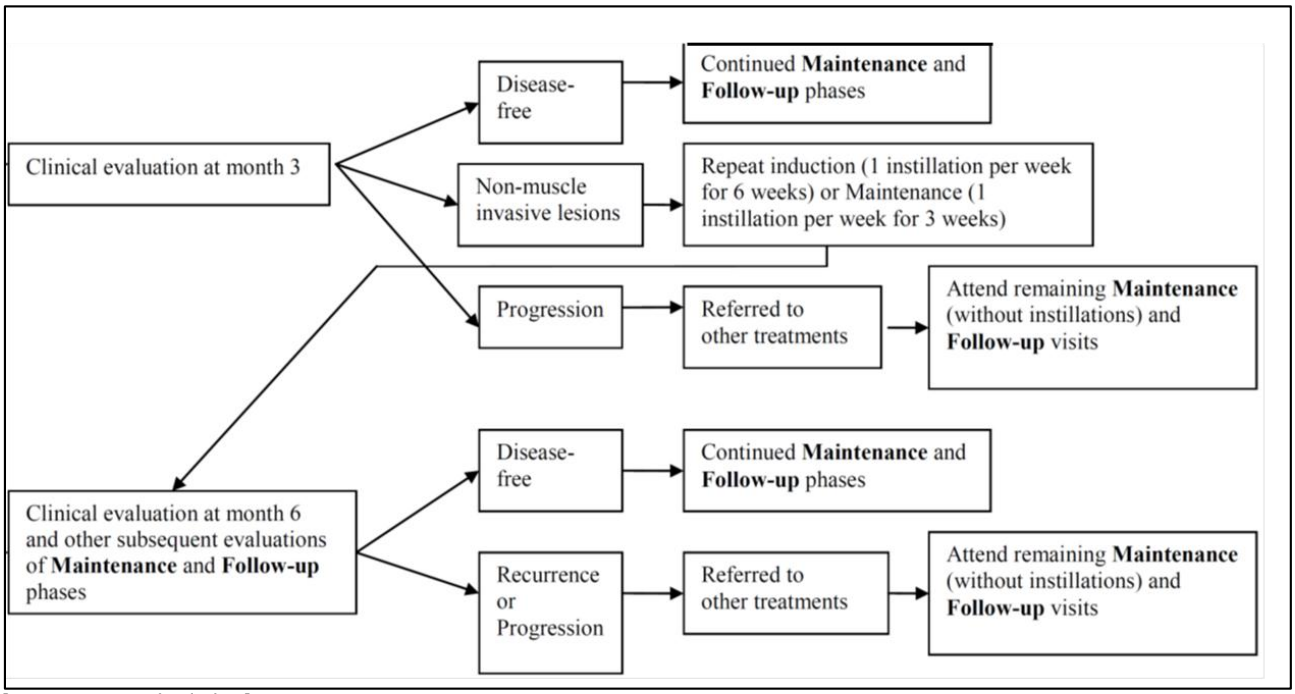
End-of-study was defined as 3 months after the last subject had either received the Month-24 instillation or had discontinued the MCNA treatment, whichever occurred first.

Figure 2. Treatment Schema



[Source: BLA submission]

Figure 3. Flow Chart of Events



[Source: BLA submission]

5.4 Study Endpoints and Evaluation

5.4.1 Primary Efficacy Endpoint

The pre-specified primary efficacy endpoint was the 1-year DFS rate based on the Kaplan-Meier estimate. Disease-free survival was defined as alive without evidence of any bladder cancer.

Efficacy endpoint assessments

Assessments included cystoscopy, biopsies, and urine cytology. Cystoscopies and urine cytology were to be performed at baseline and Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 (Figure 3). Biopsies were to be performed at baseline and Month 6 for all subjects. At any point during the course of the study, TURBTs/biopsies were to be performed if the cystoscopy revealed lesions or suspicious areas. In addition, bladder biopsies were required in the event of malignant cytology. For efficacy endpoint assessment, the absence or presence of bladder cancer in the biopsied specimen(s) was to be based on the central pathology report. The highest stage and grade, according to the WHO 2004 classification, from each biopsy specimen were to be reported and used in the analysis.

The central pathologist was to report the following biopsy results:

- Recurrence: any diagnosis of NMIBC

- Progression: any diagnosis of muscle-invasive bladder cancer
- Disease-free: no evidence of bladder cancer confirmed by biopsy

Subjects with positive cytology and/or cystoscopy but no biopsy results were not to be considered as having reached an event (either recurrence or progression). In addition, any evidence of urothelial carcinoma in the upper urinary tract and/or in the prostatic urethra was not to be considered as having reached an event.

At any evaluation visit (scheduled or unscheduled), if the cystoscopy was negative but the cytology was positive (i.e., malignant), three additional voided urine samples were to be provided within one week. Cytology was to be considered positive if any one of those samples was positive. At that point, biopsies were to be performed. If biopsies were positive, then the subject was to be considered to have reached an event (progression or recurrence). If biopsies did not reveal bladder cancer, further testing was to be done to evaluate the presence of disease outside of the bladder. As stated above, these subjects would not be considered as having reached an event (progression or recurrence) even if they had tumors outside of the bladder.

FDA comment:

a. *Since bladder biopsy was not required at 1 year, not every subject had bladder biopsy at 1 year. Thus, in some subjects, the disease-free status at 1 year, defined as no evidence of bladder cancer confirmed by biopsy, could not be based on a biopsy. Instead, disease-free status in these subjects was inferred from negative cystoscopy and/or cytology. Thus, the absence of biopsy in these subjects raises concern regarding the validity of the primary endpoint in these subjects.*
b. *The protocol specified that biopsies should be obtained if cytology was positive, even if cystoscopy was negative. However, these biopsies were not uniformly performed. Absence of such biopsies may cast some doubt regarding the disease-free status in these subjects.*

Determination of DFS Duration

DFS duration was defined as the number of days from the first dose of MCNA to recurrence, or progression, or death, whichever came first.

Censoring rules are described in Section 5.5.2.

FDA comments:

a. *In a single-arm trial without a concurrent control, a time-to-event endpoint such as DFS is generally difficult to interpret.*
b. *DFS in oncology is usually defined as the time from when a subject is found to have no disease until disease recurrence or death. Thus, the Applicant's definition of disease-*

free survival may not reflect what is commonly used in oncology trials. Subjects with CIS-containing disease at enrollment did not have their tumors resected; therefore, these subjects were not disease-free when the first dose of MCNA was administered. In contrast, subjects with papillary-only disease had their tumors resected within 56 days prior to the 1st MCNA treatment; therefore, these subjects were disease-free at the time when the first dose of MCNA was administered.

5.4.2 Secondary Efficacy Endpoints

Secondary endpoints included DFS rates at 3 months, 6 months, and 2 years, time to progression, and overall survival. Assessment modalities and schedules were the same as those for the primary efficacy endpoint.

Time to progression (TTP) was defined as the number of days from the first dose of MCNA to progression. The same censoring rules apply for TTP as for DFS, described in Section 5.5.2.

Overall survival of a subject was defined as the number of days from the first dose of MCNA to death. For a subject who was alive at study termination, the survival time was censored at the last time the subject was known to be alive.

5.5 Statistical Considerations

5.5.1 Analysis Populations

- Efficacy population:
  - Intention-to-treat (ITT) population was to include all enrolled subjects in Study 301. "Enrolled subjects" referred to all patients who provided signed informed consent, met all inclusion/exclusion criteria, and received at least one dose of MCNA.
  - Modified ITT (mITT) population was to include all enrolled subjects whose eligibility for the study was confirmed by central pathology.
  - Per-Protocol (PP) population was to include the subjects who were in the mITT and met all of the following additional criteria:
    - No major inclusion/exclusion criteria violation;
    - Received at least 5 instillations during the Induction Phase;
    - Retained MCNA for at least 45 minutes prior to voiding for 80% of all instillations received
    - Had at least one post-baseline central pathology report.

The primary efficacy endpoint, 1-year DFS rate, was to be analyzed using the ITT, mITT, and PP populations. The ITT population was the primary analysis population. All other efficacy

endpoints (DFS at 3 months, 6 months, and 2 years, duration of DFS, TTP, and OS) were to be analyzed using the ITT population.

- Safety population was to include all subjects from Study 301 and 303 who received at least one instillation of MCNA.

5.5.2 Efficacy Analysis Method

The overall duration of DFS, TTP, and OS were to be calculated by the Kaplan-Meier technique [23] and a 95% confidence interval for DFS rate at 1 year using the log-log transformation estimate of the standard error. SAS® (9.2 or later version) was to be used to perform the survival analyses.

For the analysis of the primary efficacy endpoint using the Kaplan-Meier method, the event, disease-free duration and censoring/event indicator are defined below:

Event: Subjects were to be considered as having reached an event if they had either recurrence, progression, or death.

Disease-free duration: Disease-free survival of a subject was defined as the number of days from the first dose of MCNA to recurrence, progression, or death, whichever came first.

Censoring/event indicator:

A. Early termination of treatment:
   For subjects who were lost to follow-up, or withdrawn from the study, or study termination occurred before any recurrence, progression, or death, the DFS was to be censored at the last tumor evaluation (latest of biopsy, cystoscopy and urine cytology);
B. New anti-cancer treatment:
   For subjects who started a new anti-cancer treatment (chemotherapy, immunotherapy, or radiotherapy), the DFS was to be censored at the last tumor evaluation before the start of the new anti-tumor therapy;
C. Cystectomy:
   i. For subjects who underwent cystectomy without a prior biopsy documented, the DFS was to be censored at last tumor evaluation before the cystectomy;
   ii. For subjects who underwent cystectomy with biopsy, the biopsy became the last tumor assessment and a subject could have an event or be censored at the date of cystectomy, depending on the biopsy finding. The time of cystectomy/biopsy was considered an event if the biopsy was positive; the subject was censored at the time of cystectomy if the biopsy was negative.
D. Tumor evaluation at different time points, determination of DFS:
   a. For a subject with resected papillary-alone disease at baseline, if there was any low-grade papillary tumor recurrence at Month 3 and the subject continued treatment, but

the tumor persisted at Month 6, then the disease-free status would be considered to have ended at Month 3. DFS duration of this subject would be 3 months and the subject was to be considered as having an event.

b. For a subject with CIS-containing disease at study entry, if CIS persisted during the MCNA treatment at any time, the DFS duration was to be considered as zero and the subject was considered as having an event.

FDA comments on primary efficacy analysis: The definition of disease-free survival and the censoring/event indicator violate the assumptions of the Kaplan-Meier method, making the results derived from this method difficult to interpret.

1. *Subjects with CIS were not disease-free at the study entry, but if they became disease-free later, the disease-free duration was calculated from the study entry to the time of documented event (recurrence, progression or death). This method over-estimates the disease-free duration of CIS-containing subjects and as a result, over-estimates the disease-free survival rate at 1 year. In addition, those subjects with CIS would not be at risk of recurrence until the date they became disease-free, which violates the assumption of the Kaplan-Meier method that all the subjects are at risk of the event at study entry.*
2. *Subjects who started a new anti-cancer therapy or underwent cystectomy without a documented prior biopsy or with a negative prior biopsy would be censored at the time of the last tumor assessment prior to beginning the new therapy or cystectomy. However, starting a new anti-cancer therapy or cystectomy was usually a result of disease progression; therefore, these subjects should be considered as having experienced an event rather than being censored. Thus, this censoring was very likely to be informative and therefore raises concern of bias.*

6 Study 301 Population and Subject Disposition

The study period was from November 07, 2006 to December 03, 2011, when the study was closed due to the transfer of the IND sponsorship. At the time of closure, no subjects were still receiving treatment. The median follow-up time for subjects was 43 months.

6.1 Study Populations

The primary efficacy analysis was based on the ITT population of 129 subjects.

The Safety Population includes all Study 301 and Study 303 subjects who received at least one dose of MCNA.

6.2 Subject Characteristics

Of 129 subjects enrolled, 95 (73.6%) were men and all were white. The median age was 71 years (range 40 to 90 years). The baseline demographics at enrollment are shown in Table 4.

Table 4. Baseline Demographics for Study 301

	Total N=129
Age (years)	
Median	71
Min, Max	41, 90
Gender	
Male	95 (73.6%)
Female	34 (26.4%)
Race	
White	129 (100%)
Ethnicity	
Hispanic or Latino	2 (1.6%)
Non-Hispanic or Latino	127 (98.4%)
Baseline tumor type per local pathology	
Papillary Only	50 (38.8%)
CIS only	54 (41.9%)
CIS and Papillary	25 (19.4%)
BCG Failure Type	
BCG-relapsing	22 (17.1%)
BCG-refractory	107 (82.9%)

[Source: BLA Submission]

6.2.1 BCG-refractory vs. BCG-relapsing

All subjects enrolled were considered "refractory" by the definition of BCG-refractory described in Section 5.2.1.2. Investigators, however, were not asked to further distinguish between the BCG-refractory and BCG-relapsing populations. As commented earlier in Section 5.2.1, "BCG-relapsing" was added as a sub-category for *post hoc* analysis purposes only.

The definitions used by the Applicant to distinguish between BCG-relapsing and BCG-refractory subjects for the *post hoc* analysis were as follows:

- "BCG-relapsing" – patients who were disease-free at Month 6 following the start of BCG Induction
- "BCG-refractory" – patients who were not disease-free at Month 6 following the start of BCG Induction

By this definition, 82.9% of subjects had BCG-refractory disease and 17.1% had BCG-relapsing disease (Table 4). However, BCG-refractory and BCG-relapsing disease may have different biology, response to treatment, and prognoses.

6.2.2 Prior BCG Exposure

Prior BCG exposure was captured based on the number of prior instillations (Table 5).

Table 5. Prior BCG exposure by total number of prior instillations

Number of prior BCG instillations	Total N=129
≤6	32 (24.8%)
7 to 12	52 (40.3%)
≥13	45 (34.8%)

The median number of prior BCG instillations was 12 (range 5-33) for the ITT population (n = 129), 15 (range 9-32) in the BCG-relapsing group, and 12 (range 5-33) in the BCG-refractory group.

Table 6. Prior BCG history

Sub-population	Medians					
	Days from Original Dx to MCNA Dose 1	Days from Last BCG to MCNA Dose 1	BCG induction courses #	BCG maintenance courses #	BCG total instillations #	Duration of previous BCG (days)
DFS 1 yr (27 subjects)	674	186	1	1.5	12	67
Non-DFS 1 yr (102 subjects)	678	208	2	2	12	73
BCG-Relapsing (22 subjects)	1053	190.5	1	2.5	15	94
BCG-Refractory (107 subjects)	653	206	2	1	12	72

[FDA Analysis] Dx = diagnosis; # = number

6.2.3 Discrepancies between local and central pathologists with regard to baseline NMIBC histologies

FDA reviewed all baseline pathology reports, including case report form (CRF) entries and local and central pathology reports, for all subjects. There were 31 pathology reports discrepant

between local and central pathology. The most common discrepancy was that central pathology identified more subjects with CIS and papillary disease. FDA review of fourteen of these discrepancies resulted in a change from papillary alone to "CIS-containing (CIS alone plus CIS and papillary disease)". There were also 9 central pathology reports ("unconfirmed") that either identified no tumor present, low-grade papillary only, or muscle-invasive disease, which would have disqualified the subject from eligibility (Table 7). The Applicant analyzed disease-free status based on local and central pathology separately, and eliminated several subjects from the ITT population based on central pathology findings on review of baseline pathology.

Table 7. Discrepancies between Local and Central Pathology

		Local Pathology		
		CIS	CIS and PAP	PAP Only
Central Pathology	CIS	47	4	3
	CIS and PAP	2	19	11
	PAP Only		2	32
	Unconfirmed	5		4

[FDA analysis] CIS: Carcinoma in situ; PAP: papillary disease.

The Applicant cited several reasons for these discrepancies; most notable were differences in the samples evaluated. For example, some local pathologists were unable to release diagnostic specimens to central pathology for review.

FDA reviewed the original pathology reports and determined the "FDA-determined baseline pathology" as follows:

- If local = CIS, and central = CIS; then FDA = CIS
- If local = PAP; central = PAP; FDA = PAP
- If local = CIS; central = PAP; FDA = CIS +PAP (BOTH)
- If local = PAP, and central = CIS; then FDA = CIS + PAP (BOTH)
- If either stated BOTH, then FDA = BOTH
- If central = unconfirmed, the local pathology determination was used

Table 8. Baseline Pathology Determination

Baseline Tumor Type	Local Pathology	Central Pathology	FDA Review
CIS only	54	54	52
CIS + PAP	25	32	41
CIS Containing (CIS, CIS + PAP)	*79*	*86*	*93*
Papillary Only	50	34	35
Unconfirmed		9	

[FDA analysis] CIS: Carcinoma in situ; PAP: papillary disease.

Upon FDA review of local and central pathology reports, there were 6 pathology reports that were discrepant from the histology noted in the case report form (CRF). Review of two of these reports changed the baseline pathology determination from CIS-containing to papillary-only, and two changed from papillary-only to CIS-containing. The other two did not change CIS status.

The discrepancies among local pathology, central pathology, and FDA review findings on histology could lead to uncertainty regarding the histology types in some subjects and may affect the interpretation of the study results. However, the impact of these discrepancies on the primary efficacy endpoint did not appear to be substantial (See Section 7.1.2 below).

6.2.4 Subject Disposition

Among the 129 subjects in the ITT population, 17.1% completed the protocol-specified 2-year treatment, and 82.9% terminated treatment early. The major reasons for study withdrawal were primarily the study being terminated by the Applicant (58.9%), death (17.8%), and subject withdrawal (14.0%). The high percentage of subjects who ended study due to study termination by the Applicant makes it difficult to interpret secondary and exploratory endpoints such as development of metastatic bladder cancer and cystectomy rates.

6.2.5 Protocol Deviations

Thirty-six subjects (36; 27.9%) had at least 1 protocol deviation or violation. Thirty-four eligibility violations were reported for 31 subjects, and protocol deviations were reported in 5 subjects. In general the protocol deviations and violations were minor and did not affect the integrity of the study results.

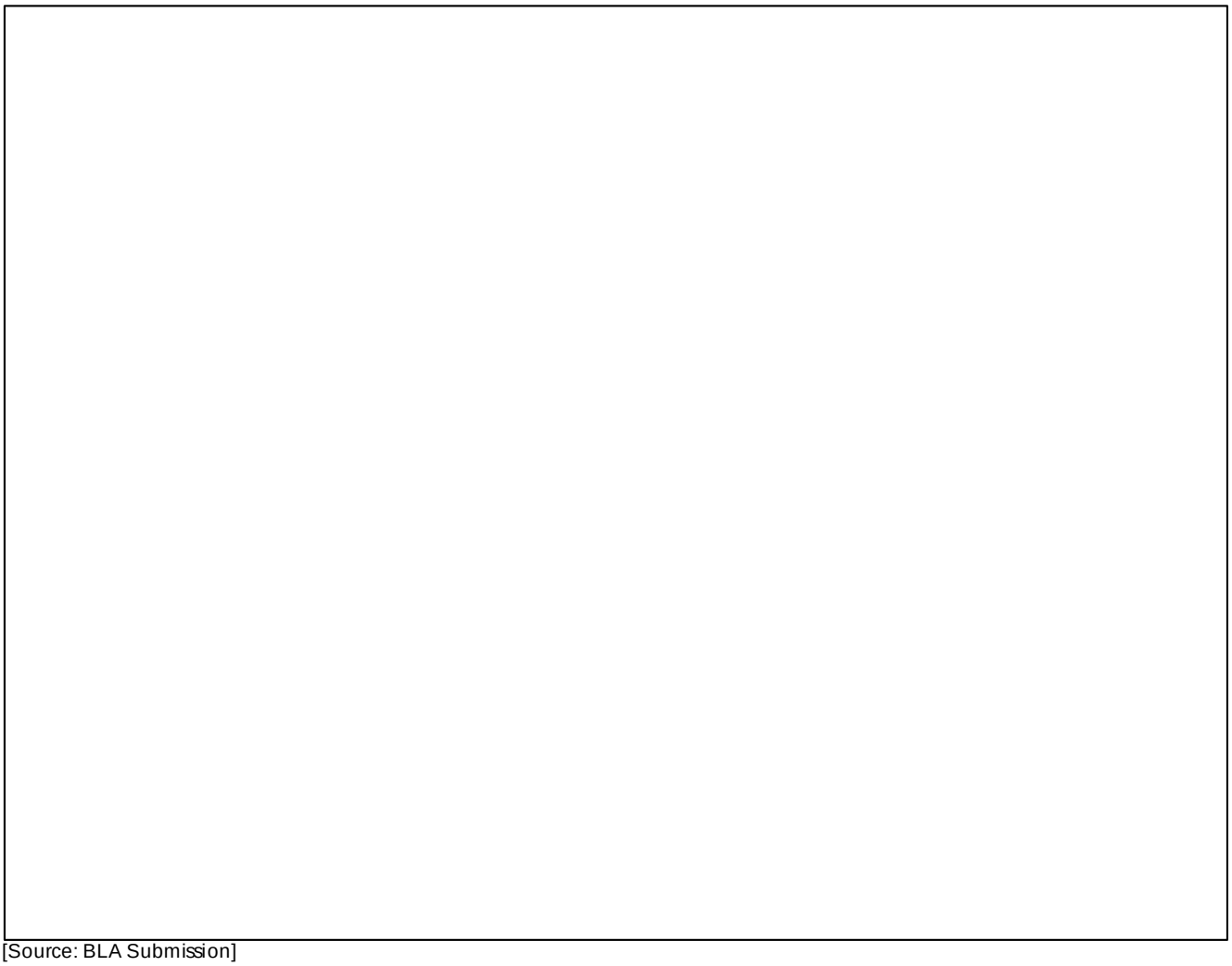
7 Efficacy Results

7.1 Primary Endpoint

7.1.1 The Applicant's Results

The primary endpoint, DFS 1y, was 25% (95% CI: 17.7% -33.0%) in the ITT population. The Applicant reported a median duration of DFS of 175 days (range 163-182) (Figure 4). Thus, Study 301 failed to meet its stated primary study objective of demonstrating that the 1-year disease-free survival rate was not lower than 40% by Kaplan-Meier estimate.

Figure 4. Applicant's DFS in the ITT Population



[Source: BLA Submission]

7.1.2 FDA analyses

As discussed in Section 5.5.2, the Applicant used a time-to-event analysis (Kaplan-Meier method), which may over-estimate disease-free duration, particularly for those subjects with CIS who were not disease-free at the trial entry, and thereby introduce a bias into the treatment effect estimate. Given the above limitations of the Kaplan-Meier method (Section 5.5.2), FDA used a separate efficacy landmark analysis to estimate the proportion of subjects who were disease-free and alive at one year.

FDA Evaluation of subjects who were disease-free and alive at 1 year (DFS 1y)

The Applicant reported 29 subjects as having DFS 1y. FDA reviewed all available data for these 29 subjects, including CRFs, datasets and original pathology reports. FDA assessed two of these 29 subjects as not having DFS 1y.

- One subject enrolled with CIS + PAP (per FDA review) had a negative biopsy at Month 6, but had positive cystoscopy and cytology (emergence of malignant cells) at both 9 and 12 months. The investigator deferred bladder biopsy at 9 months and the subject refused biopsy at 12 months and at that time was taken off study to pursue alternative therapy for bladder cancer. Therefore, FDA considers this subject as not disease-free at 1 year (non-DFS 1y).
- The other subject, with CIS (per FDA review), had a negative biopsy at Month 6, but had a positive biopsy for low-grade PAP at both 9 and 12 months. As per protocol, the subject was eligible to continue treatment with MCNA at the investigator's discretion, but should have been considered to have had a recurrence at the time of development of low-grade disease (Month 9), thus should not have been considered as DFS 1y.

Therefore, FDA considers that 27 subjects were DFS 1y.

Primary Endpoint Results (ITT population)

According to the FDA analysis, the primary endpoint of DFS 1y was 20.9% (95% CI: 14.3% - 29.0%), using a responder landmark analysis in the ITT population (Table 9). Table 9 also shows DFS 1y for subjects in subgroups (disease type and BCG failure type).

Table 9. FDA Primary Endpoint DFS 1y Responder Landmark Analysis

Population	DFS 1y	Total	Proportion	95% Confidence Interval
ITT	27	129	20.9%	(14.3%, 29.0%)
Disease Type				
CIS-containing	17	93	18.8%	(11.0%, 27.7%)
Papillary-only	10	36	27.8%	(14.2%, 45.2%)
BCG Failure Type				
BCG-Relapsing	8	22	36.4%	(17.2%, 59.3%)
BCG-Refractory	19	107	17.8%	(11.0%, 26.3%)

[FDA Analysis]

The FDA analysis supports that the DFS 1y was less than 40%.

Impact of discrepancies between local and central pathology review on DFS 1y

As discussed in Section 5.2.3, discrepancies between local and central pathology review could lead to uncertainty regarding the tumor histologies the subjects had at baseline, affecting the interpretation of the trial results. However, impact of such discrepancies on DFS 1y appears to be minimal. For example, DFS 1y for subjects with CIS-containing disease was 17.7% by local pathology, and 16.3% by central pathology, using a responder landmark analysis.

7.1.3 Duration of DFS beyond one year

The Applicant defined the duration of disease-free status of a given subject as the number of days from the first dose of MCNA to recurrence, progression, or death, whichever came first. This approach might be reasonable for subjects who had resected papillary disease only; however, this approach may not be appropriate for subjects with CIS who were not disease-free at the trial entry.

According to the FDA analysis, the median duration of DFS in the ITT population was 175 days. The median DFS duration in the DFS 1y group versus the non-DFS group at 1 year, was 1182 days and 111 days, respectively. The median follow-up time in the ITT population was 43 months. Therefore, of the subjects that maintained DFS status at one year, several did so for a prolonged period of time, thus retaining their bladder for an extended period of time. In addition, those who had an event and therefore were not likely to benefit appear to have gone on to alternate therapy such as cystectomy.

The swimmers plot in Figure 5 shows the outcomes for all 129 subjects at the time of study termination or censoring. The subjects with papillary-only disease are represented by the blue lines, and subjects with CIS-containing disease are indicated by the yellow lines. Events are indicated by black circles and censored events by open diamonds. Finally, where follow-up was reported, the time of metastatic disease occurrence is indicated by the X and time of cystectomy by the U. As seen in Figure 5, no metastatic disease was identified prior to Month 6. Further discussion regarding the development of metastatic bladder cancer in the study population can be found in Section 8.2.4. Additionally, the cystectomy rates were much higher in the non-DFS 1y group (50%) versus the DFS 1y group (17%), though follow-up was limited.

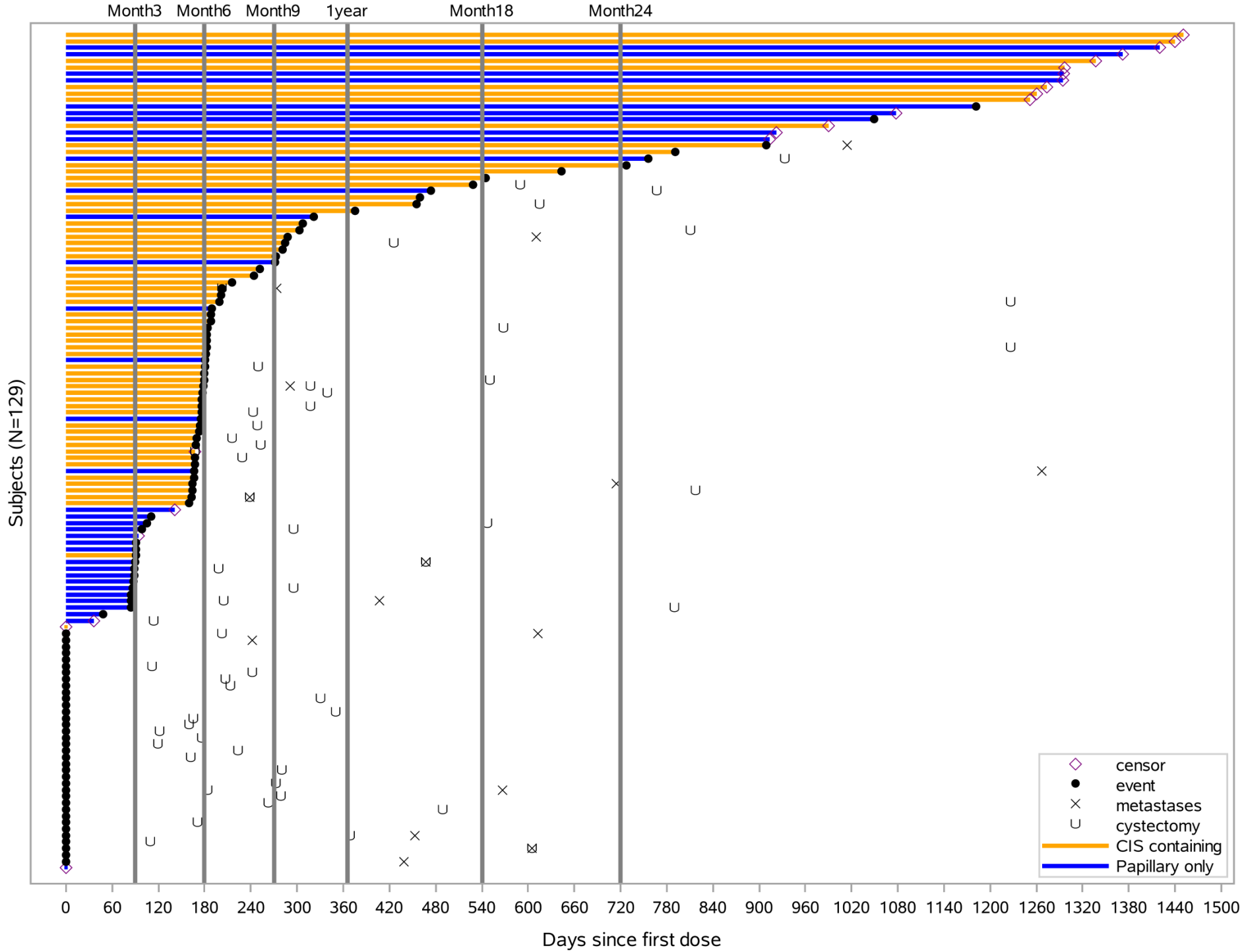


Figure 5. Swimmer's Plot of all Subjects of Study 301

Nineteen subjects who were DFS 1yr continued to have no evidence of disease through Month 24, and 18 of those did not undergo cystectomy while on study or in follow-up. Although the follow-up was limited, the median time to cystectomy was considerably prolonged for the DFS 1y group compared to the non-DFS 1y group (Section 7.3).

7.2 Secondary efficacy endpoints

Secondary efficacy endpoints included DFS at 3, 6 and 24 months, TTP and OS in the ITT population. However, because of the high amount of censoring due to early termination of the trial, the Applicant was unable to determine the median TTP or OS. The DFS% (95% CI) at 3, 6 and 24 months for the ITT population was 68.9 (60.1 - 71.3), 38.4 (29.8 – 46.9), and 19.0 (12.6 – 26.5), respectively.

7.3 Cystectomy rates

Fifty-five subjects (43%) underwent cystectomy, 51/102 (50%) in the FDA non-DFS 1y group and 4/27 (14.8%) in the DFS 1y group. Of these 55 subjects, 44 had CIS-containing disease and 11 were papillary-only according to FDA evaluation of baseline pathology reports. The median time to cystectomy was 767 days in the DFS group and 263 days in the non-DFS 1y group. These data, however, are difficult to interpret due to the limited follow-up of subjects and missing information. For example, in the 27 subjects in the DFS 1y group, 4 cystectomies were reported and 8 subjects were reported to have “no cystectomy”; however, there were no cystectomy data captured in the CRFs of the remaining 15 subjects.

7.4 MCNA treatment effect in subjects with CIS-containing disease

As discussed in Section 10 below, deficiencies in the trial design of Study 301 and its failure to meet the stated objective make it very difficult to estimate the treatment effect of MCNA for the proposed indication. However, an evaluation of CIS-containing disease to MCNA treatment and resultant CR could indicate MCNA’s treatment effect, since CIS-containing disease does not usually undergo spontaneous regression. Therefore, FDA examined the complete response in this subpopulation of subjects with baseline CIS-containing disease. Specifically, FDA considered the CR rate at 6 months and CR duration for 93 subjects with CIS-containing disease at baseline. Although not part of the original trial design, FDA chose a CR rate at 6 months, because all subjects underwent mandatory bladder biopsy at that time point, so that the absence of bladder cancer could be evaluated with relative certainty.

Figure 6 shows a swimmer’s plot for the 93 subjects with baseline CIS-containing disease and 25 CRs at 6 months. The blue lines represent the duration of disease presence from the onset of the MCNA treatment. The yellow lines represent the duration of complete response. Events are indicated by black circles and censored subjects by open diamonds. Where follow-up was

reported, the time of metastatic disease occurrence is indicated by the X and time of cystectomy by the U. The number on the far right of the plot corresponds to the number of BCG instillations each subject received prior to the 1st dose of MCNA. The asterisk denotes subjects who were categorized as BCG-relapsing. The vertical dashed lines denote the follow-up time points.

As seen in Figure 6, 25 of 93 [26.9%, (95% CI 17.9%, 35.9 %)] subjects with baseline CIS-containing disease experienced a CR confirmed by bladder biopsy at 6 months. The median duration of CR was 455 days (15.1 months) from the time when subjects first achieved CR and 18.1 months from start of MCNA treatment to the last evaluation that did not identify the recurrence of any bladder cancer. The median number of prior BCG instillations was 12. Four of these 25 CRs (16%) had cystectomy and 2 additional subjects without cystectomy developed metastatic bladder cancer. Seven of the 10 subjects with the longest CR duration (>24 months) had their CRs censored at study termination. In contrast, 40 of 68 (58.8%) subjects who did not have CR at 6 months had cystectomy, and 9 of these 68 developed metastatic bladder cancer.

These results appear to indicate an MCNA treatment effect in that 1 in 3-4 subjects with CIS-containing disease had CR at 6 months without cystectomy. Some of these responses appeared to be durable: 10 of 25 CRs lasted beyond 2 years (Figure 6). As discussed in Section 10.6, because of considerable morbidity associated with cystectomy, these subjects who avoided or delayed cystectomy could be considered as having gained some benefit from the MCNA treatment. However, these durable responses need to be considered with the following caveats. Five of these 10 were categorized as BCG-relapsing prior to MCNA treatment. As discussed earlier in Sections 6.2.1 and 10.3.2 below, BCG-relapsing subjects may have a better prognosis. In addition, it is unknown whether these subjects might have responded to BCG if they had been given more BCG instillations. Three of these 10 had received only 6 and 9 BCG instillations prior to MCNA, respectively, raising the question whether these subjects were truly BCG-refractory since they did not receive 2 prior induction courses. In addition, as discussed in Section 10.2.1 below, the absence of bladder biopsy at the last tumor evaluation for these subjects calls into question whether these subjects were truly in CR when they were censored at the study termination. Therefore, the assessment of clinical meaningfulness of these durable responses should consider the above limitations.

Nonetheless, overall CR rate at Month 6 and CR duration in subjects with CIS-containing disease who received MCNA appeared to be comparable to those reported for valrubicin in a similar patient population (18% complete response documented by bladder biopsies and cytology at 6 months following initiation of valrubicin therapy; 13.5-month median duration of response from start of treatment to last bladder biopsy without tumor [15]).

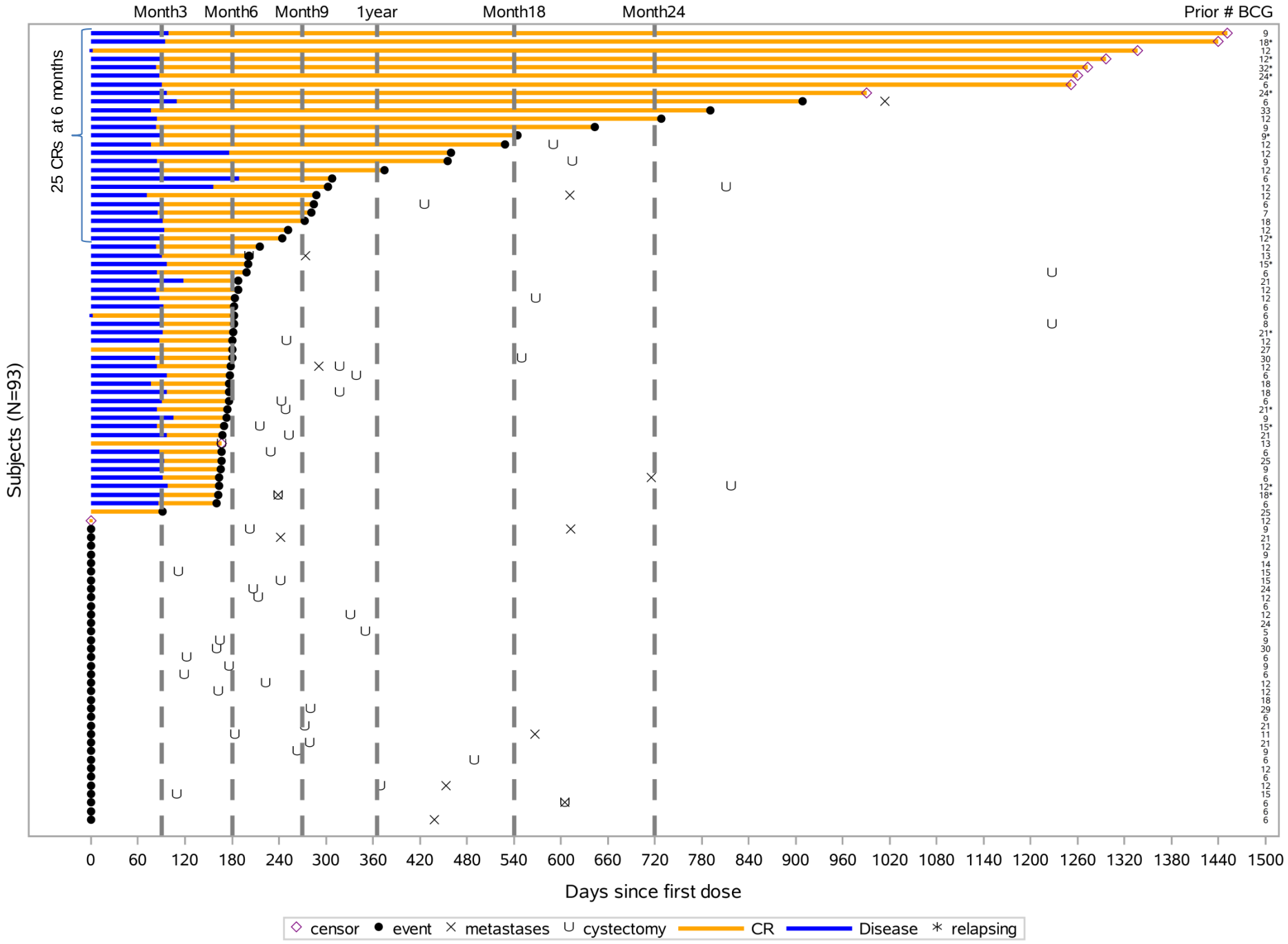


Figure 6. Subjects with CIS-containing Disease at Baseline and 25 CRs at 6 Months

7.5 Efficacy summary

- The FDA determined DFS 1y was 20.9% in the ITT population, using a responder landmark analysis, confirming that Study 301 did not meet its stated objective of demonstrating DFS 1y not less than 40%.
- In a subpopulation of 93 subjects with baseline CIS-containing disease, treatment with MCNA was associated with a 27% CR rate at 6 months with a median duration of 15.1 months.

8 Safety Results

The safety population includes 129 subjects in Study 301 and 37 subjects in Study 303 who received at least one dose of MCNA.

Study 303 was a Phase 3, randomized, active-controlled, open-label, multi-center study designed to evaluate the safety and efficacy of MCNA in comparison with mitomycin C in the treatment of subjects with NMIBC who had failed prior BCG therapy. This trial was terminated early in November 2012 due to logistic issues. At the time of termination, 82 subjects were treated under Study 303, including 37 subjects treated with MCNA, and 45 subjects treated with mitomycin C.

Safety was evaluated based on recorded adverse events (AEs), physical examinations, and clinical laboratory assessments. If a subject experienced multiple episodes of a single adverse event, the greatest severity and strongest investigator assessment of relation to MCNA was assigned to the adverse event. Demographics and disease status of the safety population are shown below in Table 10.

Table 10. Demographics and Disease Status of the Safety Population

	Study 301 N=129	Study 303 N=37	Combined N=166
Age (years)			
Median	71	75	72
Min, Max	41, 90	59, 90	41, 90
Gender			
Male	95 (73.6%)	32 (86.5%)	127 (76.5%)
Female	34 (26.4%)	5 (13.5%)	39 (23.5%)
Race			
White	129 (100%)	37 (100%)	166 (100%)
Ethnicity			
Hispanic or Latino	2 (1.6%)	1 (2.7%)	3 (1.8%)
Non-Hispanic or Latino	127 (98.4%)	36 (97.3%)	163 (98.2%)

	Study 301 N=129	Study 303 N=37	Combined N=166
Baseline disease characteristics			
Papillary Only	38 (29.5%)	19 (51.4%)	57 (34.3 %)
CIS only	59 (45.7%)	13 (35.1%)	72 (43.4%)
CIS and Papillary	32 (24.8%)	5 (13.5%)	37 (22.3%)
BCG Failure Type			
Relapsing	22 (17.1%)	18 (48.6%)	40 (24.1%)
Refractory	107 (82.9%)	19 (51.4%)	126 (75.9%)
Prior Therapy			
Intravesicular BCG	129 (100%)	37 (100%)	166 (100%)
Intravesicular Mitomycin C	42 (32.7%)	2 (5.4%)	44 (26.5%)
Intravesicular Interferon	1 (0.8%)	5 (13.5%)	6 (3.6%)
Other Intravesicular chemotherapy	3 (2.3%)	3 (8.1%)	6 (3.6%)
Other Intravesicular immunotherapy	-	5 (13.5%)	5 (3.0%)
Other treatment	-	1 (2.7%)	1 (0.6%)

For Study 301, in addition to the mandatory qualifying BCG therapy, 46 subjects (35.7%) received previous intravesical chemotherapy or immunotherapy, including 1 (0.8%) subject who received interferon, 42 (32.7%) subjects who received mitomycin C, and 3 (2.3%) subjects who received other intravesical chemotherapy (Table 10).

For Study 303, in addition to the mandatory qualifying BCG therapy, 16 (43.2%) subjects had received other prior intravesical chemotherapy or immunotherapy, including another type of immunotherapy in 5 (13.5%) subjects, intravesical interferon in 5 (13.5%) subjects, intravesical mitomycin C in 2 (5.4%) subjects, another type of intravesical chemotherapy in 3 (8.1%) subjects, and another treatment in 1 (2.7%) subject (Table 10).

8.1 Drug Exposure

Median duration of treatment for Study 301 was 156 days (range 1-783 days), and 92 days (range 14-372 days) in Study 303 (Table 11).

Table 11. MCNA Exposure

	Study 301	Study 303
Subjects (n)	129	37
Time on treatment (days)		
Median	156	92
Min, Max	1, 783	14, 372
Time in trials (days)		
Median	1035	230
Min, Max	28, 1837	81, 618

Number of received doses		
Median	12	7
Min, Max	1, 24	3, 16
Retention time (minutes)		
Median	125	65
Min, Max	9, 270	45, 250

[Source: FDA Analysis]

Exposure to MCNA occurred at one dose level (8 mg per instillation).

According to the protocol for Study 301, each subject was to receive a maximum of 24 instillations: 6 weekly instillations during the induction phase, followed by 3 or 6 weekly instillations at Month 3, and then 3 weekly instillations repeated at Months 6, 12, 18, and 24. According to the protocol for Study 303, each subject was to receive a maximum of 16 instillations; 6 weekly instillations during the induction phase, followed by 1 monthly instillation for 10 months (Months 3 – 12).

For Study 301, the median number of instilled doses was 12. For Study 303, the median number of instilled doses was 7. For Study 301, the median MCNA retention time was 125 minutes. For Study 303, the median retention time was 65 minutes.

8.2 Adverse Events in Study 301 and 303 Safety Analysis

8.2.1 Definitions

Treatment-emergent adverse event (TEAE): any adverse event that occurred between the first MCNA treatment date and the last MCNA treatment date plus 35 days, per protocol.

Adverse Events were graded as CTCAEv3.0 Grade 1 through 5, with Grade 5 being death. A serious adverse event was any untoward medical occurrence, regardless of grade, that resulted in death, was life-threatening, required or prolonged hospitalization, resulted in significant disability/incapacity, constituted a congenital anomaly/birth defect, or was medically significant, per protocol.

8.2.2 TEAEs

As noted above, the median exposure to MCNA was substantially greater for subjects in Study 301 compared to subjects in Study 303. In addition, the primary evidence of MCNA effectiveness comes from Study 301. Thus, subjects in Study 303 may have received less exposure to MCNA, which limits the value of their safety data, particularly for the assessment of common adverse events. Therefore, the safety profile of MCNA with regard to common TEAEs is based primarily on Study 301.

The incidence of TEAEs from Study 301 is described in Table 12. A total of 118 subjects (91.5%) exposed to MCNA had at least one TEAE. Overall, 18 subjects (14%) experienced treatment-emergent adverse events that were considered serious (Section 8.2.3). The nature and frequency of common TEAEs were similar in Study 303 to Study 301.

Table 12. Summary of Treatment-Emergent Adverse Events

	Study 301 N=129
TEAEs	118 (91.5%)
Treatment-emergent SAE	18 (14%)
Fatal TEAE	3 (2.3%)
TEAE leading to drug withdrawal	3 (2.3%)
TEAE leading to dose delay	11 (8.5%)

[Source: FDA Analysis]

Most TEAEs were Grade 1 and 2 (Table 13).

Table 13. TEAEs Maximum Toxicity Grade

	Study 301 N=129
Any treatment-emergent adverse event	118 (91.5%)
Grade 1	39 (30.2%)
Grade 2	57 (44.2%)
Grade 3	18 (13.9%)
Grade 4	1 (0.8%)
Grade 5	3 (2.3%)

[Source: FDA Analysis]

The most frequent treatment-emergent adverse events from Study 301 are shown in Table 14. The most common adverse events include hematuria, dysuria, fatigue, UTI, pollakiuria, and micturition urgency.

Table 14. Most Frequent TEAEs (occurring in >= 5% Subjects exposed to MCNA)

Treatment-Emergent Adverse Events	Study 301 N=129
Any treatment-emergent adverse event	118 (91.5%)
Hematuria	47 (36.4%)
Dysuria	42 (32.6%)
Fatigue	28 (21.7%)
Urinary tract infection	25 (19.4%)
Pollakiuria	23 (17.8%)
Micturition urgency	17 (13.2%)
Back pain	11 (8.5%)
Cough	11 (8.5%)
Headache	10 (7.7%)
Nausea	10 (7.7%)

Treatment-Emergent Adverse Events	Study 301 N=129
Nasopharyngitis	9 (7%)
Oedema peripheral	9 (7%)
Asthenia	8 (6.2%)
Diarrhea	8 (6.2%)
Nocturia	8 (6.2%)
Anxiety	7 (5.4%)
Arthralgia	7 (5.4%)
Dizziness	7 (5.4%)
Dyspnoea	7 (5.4%)
Insomnia	7 (5.4%)
Nasal congestion	7 (5.4%)
Pyrexia	7 (5.4%)

[Source: FDA Analysis]

8.2.3 Serious Adverse Events

Treatment-emergent serious adverse events occurred in 20/166 subjects (12%) in the safety population. The most common treatment-emergent serious adverse events were hematuria in three subjects (1.8%) and syncope in two subjects (1.2%).

8.2.4 Adverse Events of Special Interest

Secondary Primary Cancer

Forty-eight (37.2%) subjects in Study 301 developed secondary primary cancers, as shown in Table 15 below.

The majority of secondary primary cancers originated from the genitourinary system, including the prostate and urothelium. For comparison, based on literature reports on secondary primary cancers, approximately 20% of previously aggressive bladder cancer relapses occurred outside the bladder in the upper urinary tract, and 16% in the prostate [6, 24].

Table 15. Secondary Primary Cancer

	Study 301 N=129
Total secondary primary cancer	48 (37.2%)
Genitourinary Malignancy*	
Prostate cancer	23 (17.8%)
Ureteric cancer	23 (17.8%)
Urethral cancer	6 (4.7%)
Renal pelvis cancer	1 (0.8%)
Renal cell carcinoma	1 (0.8%)
Other malignancies	12 (9.3%)

[Source: FDA Analysis *some subjects had more than one cancer type.]

Metastatic Bladder cancer

Non-responders to BCG therapy at 6 months have a high risk (greater than 90%) of progression to muscle-invasive disease. No more than 2 induction courses of BCG are recommended, as there is a 7% actuarial risk of progression to muscle invasive disease with each additional course [6]. Thus, as discussed in Section 2.2.3, cystectomy is strongly recommended for treatment of high-risk patients failing BCG, and delay in cystectomy has been shown to result in a poor prognosis [6, 14]. However, cystectomy is associated with significant morbidity, mortality and quality-of-life detriment [25]. Therapies such as intravesical MCNA that have the potential to delay cystectomy could avoid its attendant morbidity and thus be beneficial to these subjects. Conversely, delaying cystectomy in patients with high-risk disease could increase the risk of disease progression and potentially permit subsequent development of metastatic bladder cancer (MBC). To further evaluate this issue, FDA examined the cases of MBC reported from Study 301.

As shown in Table 16, 15 (11.6 %) subjects developed MBC in Study 301. Days from 1st MCNA instillation to MBC diagnosis ranged from 239 days to 1267 days. Eighty percent (12/15) had baseline CIS-containing and 20% (3/15) papillary-only disease, according to FDA analysis of baseline pathology reports. Five subjects underwent cystectomy prior to MBC diagnosis. Of those 15 subjects, only 1 subject achieved disease-free status at 1 year; this subject subsequently developed MBC 1014 days after 1st MCNA instillation.

Table 16. MBC Cases

	Study 301 N=129
Total number MBC	15 (11.6%)
Days from 1st MCNA instillation	239 to 1267 days
Cystectomy prior to MBC	5 (33.3%)
Baseline pathology PAP-only	3 (20%)
Baseline pathology CIS-containing	12 (80%)
Disease-free at 1 year	1 (6.7%)

[Source: FDA Analysis]

Follow-up information is limited for many subjects because of the early closure of the trial. Because of the early study closure and the lack of a control, it is not known whether MCNA treatment and the resulting delay in cystectomy might lead to increased risk of developing MBC.

8.3 Deaths

A total of 27 deaths were reported in the safety population, all in Study 301.

Four deaths occurred during study treatment, including three deaths which occurred within 35 days after the last MCNA treatment (fatal TEAEs). The causes of these fatal TEAEs included

cerebral hematoma, multi-organ failure, and pulmonary fibrosis. The remaining subject died of cardiopulmonary arrest.

An additional 23 deaths occurred after study treatment discontinuation, and were therefore not designated as TEAEs. Progressive disease with related complication was the cause of death in 13 subjects (13/23), and the remaining 10 deaths were due to non-bladder malignancy (4), cardiovascular disease (3), respiratory failure (1), and unknown causes (2).

The deaths occurred from Days 57 to 1319 after initiation of MCNA therapy. There were no deaths attributed to MCNA treatment.

8.4 Safety summary

The adverse events associated with MCNA treatment were consistent with those observed in the use of other therapeutic intravesical agents and include the local and systemic adverse events listed below:

- 91.5% (118/129) of subjects in Study 301 had at least one TEAE.
- The most common treatment-emergent adverse events with MCNA were hematuria (36.4%), dysuria (32.6%), fatigue (21.7%), UTI (19.4%), pollakiuria (17.8%), and micturition urgency (13.2%).
- There was no death related to MCNA instillation.
- There were two MCNA-related TE-SAEs: one grade 3 UTI and one moderate hematuria.
- There were two MCNA-related TEAEs (one asthenia and one vomiting) leading to MCNA withdrawal.
- The most frequent MCNA-related systemic adverse events include fatigue (26/166, 15.7%), malaise (6/166, 3.6%), chills (5/166, 3%), pyrexia (4/166, 2.4%), nausea (4/166, 2.4%), diarrhea (4/166, 2.4%), asthenia (4/166, 2.4%), and abdominal distension (4/166, 2.4%).
- Fifteen (11.6 %) subjects developed MBC in Study 301; with days from first MCNA instillation to MBC diagnosis ranging from 239 days to 1267 days.

In summary, the majority of TEAEs from intravesical instillation of MCNA were mild or moderate in severity and localized to the bladder. There was no death related to MCNA instillation, and there were two MCNA-related SAEs including one UTI and one hematuria. Lastly, there were 15 subjects developed MBC in Study 301.

9 Overall Summary

- In this BLA, the primary evidence of effectiveness of MCNA comes from Study 301. The study subjects in this single-arm trial included subjects with NMIBC at high risk of recurrence or progression who had failed prior BCG treatment.

- FDA-determined DFS 1y was 20.9% with a median duration of 175 days, confirming that Study 301 did not meet its stated objective of demonstrating DFS 1y not less than 40%.
- In a subpopulation of 93 subjects with baseline CIS-containing disease, treatment with MCNA was associated with a 27% CR rate at 6 months with a median CR duration of 15.1 months.
- Most TEAEs observed with MCNA treatment were mild. The most common MCNA-related treatment-emergent adverse events were dysuria, hematuria, fatigue, pollakiuria, and micturition urgency.
- Fifteen (11.6%) subjects developed MBC in Study 301. There is concern that delaying cystectomy in subjects with high-risk disease could increase the risk of disease progression and subsequent development of MBC.

10 Issues and Discussions

10.1 Evidence of Effectiveness

Study 301 provides the primary evidence of the effectiveness of MCNA for the treatment of NMIBC at high risk of recurrence or progression in adult patients who failed prior BCG immunotherapy. FDA review of this BLA has identified concerns regarding both the study design and the study results. These concerns include the inherent limitations of the single-arm trial design without a concurrent control; the reliability of DFS assessments; the inability to estimate the effect size of the primary endpoint of DFS 1y; the study population and indication statement. These concerns make it very difficult to interpret the efficacy results of Study 301 and the claimed effectiveness of MCNA. However, in the 93 subjects with baseline CIS-containing disease, MCNA treatment appeared to result in a durable CR in some subjects.

10.1.1 Trial design and analysis

Study 301 was a single-arm trial evaluating the efficacy and safety of MCNA with the primary DFS 1y based on the Kaplan-Meier estimate. However, this study enrolled a mixture of subjects with CIS-containing disease and subjects with resected papillary-only disease who were at different risks for recurrence, i.e., the former had active disease and the latter had no disease at the study entry. Thus, the Applicant's analysis approach in estimating the DFS rate by combining these two different populations violated the assumption of the Kaplan-Meier method, which requires that all the subjects be at risk at the study entry. Therefore, the derived primary endpoint result was not valid.

In addition, subjects who had papillary disease alone were rendered disease-free at baseline by surgical resection. Thus, in the absence of any identifiable disease, use of MCNA in these

subjects would be considered adjuvant treatment, whereas in subjects with CIS-containing disease, MCNA was for therapeutic use. A single-arm trial without a concurrent control in such a combined patient population would not be able to adequately evaluate and interpret DFS, a time-to-event endpoint.

10.1.2 Failure to meet the stated study objective

The primary study objective was to show a true 1-year DFS of not less than 40%. However, the Applicant reported a 25% DFS1y in the ITT population. Therefore, Study 301 did not meet its stated primary objective. FDA's responder landmark analysis revealed a DFS 1y of 20% in the ITT population, confirming that MCNA's treatment effect on DFS 1y was less than 40%.

10.1.3 Inherent disadvantage of single-arm trial

In this single-arm trial without a concurrent control, a time-to-event endpoint such as DFS is difficult to interpret.

10.2 Estimate of treatment effect size

The following issues make it difficult to reliably estimate the size of MCNA's treatment effect on disease-free status at 1 yr.

10.2.1 Inadequate evaluation for DFS 1y

The definition of disease-free status required biopsy-confirmed absence of bladder cancer. Since bladder biopsy was not required at 1 year, not every subject had bladder biopsy at 1 year. Thus, in some subjects, the disease-free status at 1 year, defined as no evidence of bladder cancer confirmed by biopsy, could not be based on the biopsy. Instead, disease-free status in these subjects was inferred from negative cystoscopy and/or cytology. Thus, the absence of biopsy in these subjects raises concern regarding the validity of the primary endpoint in these subjects.

10.2.2 Uncertainty regarding the duration of DFS

The Applicant defined the duration of disease-free status of a given subject as the number of days from the first dose of MCNA to recurrence, progression, or death, whichever came first. This approach might be reasonable for subjects who had resected papillary disease only; however, this approach may not be reasonable for subjects with CIS-containing disease who were not disease-free at the trial entry.

10.2.3 Magnitude of MCNA treatment effect

With respect to the magnitude of MCNA's treatment effect, it is uncertain whether 20.9% DFS 1y is clinically meaningful when considering the activity of other investigational agents or treatment options in the intended patient population. For example, a Phase 2 trial of patients with high- (89 percent) or intermediate- (11 percent) risk disease previously treated with two or more regimens utilizing BCG reported a durable disease-free response of 28 and 21 percent at one and two-years following treatment with intravesical gemcitabine [26]. Although there are inherent limitations in comparing results of different trials, the reported disease-free response observed in gemcitabine-treated subjects appeared to be comparable with the DFS 1y in MCNA-treated subjects observed in Study 301. Therefore, it is unclear whether this observed 20.9% DFS 1y is clinically meaningful.

10.2.4 Inadequate long-term follow-up

Long-term clinical outcomes of many Study 301 subjects were unknown. Due to the early termination of the study, these subjects were not followed to 60 months as planned. Therefore, it is not known whether MCNA treatment could affect long-term clinical outcomes such as cystectomy, development of metastatic bladder cancer, and death.

10.3 Patient population

10.3.1 Study 301

Study 301 enrolled subjects with NMIBC who had CIS–containing diseases (CIS alone or CIS plus papillary) and who had papillary-alone disease. The study protocol mandated that subjects who had papillary-alone disease undergo TURBT prior to or within eight weeks of the 1st dose of MCNA treatment, rendering these subjects disease-free at or soon after the onset of the study treatment. The FDA-assessed DFS 1y (a responder landmark analysis) is 20.9% for the ITT population, 18.8% for subjects with CIS-containing diseases and 27.8% for subjects with papillary-only disease.

Inclusion of subjects with CIS-containing and papillary-only disease in the study makes it difficult to interpret DFS 1y results. Because subjects with papillary-only disease had undergone surgical resection at baseline, it is uncertain whether the disease-free status at one year reflected a treatment effect from MCNA or a result of the surgical resection. In addition, disease-free survival for subjects who have no disease at baseline is usually difficult to evaluate in the context of a single-arm trial without a concurrent control. In contrast, for subjects who had CIS-containing disease at baseline, a disease-free status at one year could indicate a treatment effect from MCNA.

10.3.2 Proposed patient population

The proposed indication for MCNA is treatment of NMIBC at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing.

The enrolled subjects in Study 301 met either one of the two eligibility criteria for BCG-refractoriness as described in Section 5.2.1.2. However, the Applicant added "BCG-relapsing" for analysis after the termination of Study 301 to denote subjects who were disease-free at Month 6 following the start of BCG induction, as opposed to "BCG-refractory" subjects who were not disease-free at Month 6 following the start of BCG induction. While Study 301 enrolled relatively fewer [22 (17%)] "BCG-relapsing" subjects, BCG-relapsing disease may have a different biology, response to treatment, and prognoses compared with BCG-refractory disease.

FDA-assessed DFS 1y was 17.8% for BCG-refractory subjects and 36.4% for BCG-relapsing subjects (Table 9). This numerically higher DFS 1y in BCG-relapsing subjects could have several possible explanations. First, BCG-relapsing subjects may have a better prognosis. Supporting this hypothesis is a recent study which showed worse outcomes for patients with BCG-refractory disease compared with those who had BCG-relapsing disease [27, 28]. Second, these BCG-relapsing subjects may have a better response to MCNA. However, it is not clear whether these subjects could have responded if they had been retreated with BCG, rather than MCNA.

10.4 subpopulation of CIS-containing disease

As discussed in Section 7.4, MCNA treatment was associated with a 27% CR at 6 months with an mDOR of 15.1 months, comparable to that reported for valrubicin, the only FDA-approved treatment for subjects with CIS disease refractory to BCG therapy. Although not pre-specified in the trial design, such an observation might provide evidence of effectiveness for MCNA. Since active CIS disease does not usually regress on its own, complete response in this setting would reflect a treatment effect from MCNA. In addition, some CRs lasted more than two years, suggesting that these subjects might have benefited by not having cystectomy with its attendant morbidity. However, it is not clear whether some of these subjects were truly refractory to BCG and whether their disease might have responded to further BCG therapy if it had been given.

10.5 Safety

Subjects of Study 301 had NMIBC at high risk of recurrence or progression and had failed prior BCG treatment. The treatment options for these subjects included cystectomy. Delaying cystectomy might predispose these subjects to develop invasive and metastatic bladder cancer

and death. Fifteen (11.6%) subjects developed metastatic bladder cancer in Study 301. However, follow-up information was limited for many subjects because of the early trial closure. Thus, it is not known whether MCNA treatment instead of cystectomy might lead to increased risk of developing metastatic bladder cancer.

10.6 Risk-benefit analysis

In a subpopulation of subjects with CIS-containing disease who received MCNA treatment, 27% of subjects experienced CR at 6 months that appeared to be durable without cystectomy. Because of the considerable morbidity associated with cystectomy, these subjects could conceivably be considered as having gained some benefit from the MCNA treatment without cystectomy. However, it is unclear whether some of these subjects could gain a similar benefit with other treatments, including retreatment with BCG.

Cystectomy is strongly recommended for patients who have high-risk NMIBC refractory to BCG. Many subjects with CIS-containing disease who did not experience CR at 6 months or who did have a CR at 6 months but did not maintain it beyond 24 months had cystectomy and some developed metastatic bladder cancer. Therefore, the questions remain whether these subjects had been placed at higher risk for developing invasive and metastatic disease by receiving the MCNA treatment rather than cystectomy upfront, and whether the treatment effect size would justify that risk.

In conclusion, it appears that patients with CIS-containing disease refractory to BCG therapy might represent a population that could benefit from MCNA therapy, i.e., some of these patients may not need immediate cystectomy. However, frequent follow-up and vigilant surveillance would be needed to mitigate the concern that delaying cystectomy may increase the risk of the development of invasive disease or metastatic bladder cancer. In the event that the CIS-containing disease persists after initial MCNA treatment, patients could be referred to have immediate cystectomy. In this context, FDA is seeking advice from this advisory committee on whether MCNA treatment has a favorable benefit-risk profile in patients with CIS-containing disease refractory to BCG therapy.

11 References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): p. 5-29.
2. Fleshner, N.E., et al., *The National Cancer Data Base report on bladder carcinoma. The American College of Surgeons Commission on Cancer and the American Cancer Society.* Cancer, 1996. **78**(7): p. 1505-13.
3. Eble, J.E., JI; et al., *World Health Organization histologic and genetic typing of tumors of the kidney, urinary bladder, prostate gland and testis.* 2004, Lyon: IARC Press.
4. Babjuk, M., et al., *EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013.* Eur Urol, 2013. **64**(4): p. 639-53.
5. Chade, D.C., et al., *Clinical outcomes of primary bladder carcinoma in situ in a contemporary series.* J Urol, 2010. **184**(1): p. 74-80.
6. Aldousari, S. and W. Kassouf, *Update on the management of non-muscle invasive bladder cancer.* Can Urol Assoc J, 2010. **4**(1): p. 56-64.
7. Amling, C.L., *Diagnosis and management of superficial bladder cancer.* Curr Probl Cancer, 2001. **25**(4): p. 219-78.
8. Sylvester, R.J., W. Oosterlinck, and A.P. van der Meijden, *A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials.* J Urol, 2004. **171**(6 Pt 1): p. 2186-90, quiz 2435.
9. Sylvester, R.J., et al., *Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials.* J Urol, 2005. **174**(1): p. 86-91; discussion 91-2.
10. UPI, T., *TheraCys USPI*. 1990, 2013, Sanofi Pasteur Limited: Swiftwater, PA, USA.
11. Lightfoot, A.J., H.M. Rosevear, and M.A. O'Donnell, *Recognition and treatment of BCG failure in bladder cancer.* ScientificWorldJournal, 2011. **11**: p. 602-13.
12. Jarow, J.P., et al., *Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop.* Urology, 2014. **83**(2): p. 262-4.
13. Guidelines, N.C.C.N.N., *Bladder Cancer* 2015: www.nccn.org/.
14. Zlotta, A.R., N.E. Fleshner, and M.A. Jewett, *The management of BCG failure in non-muscle-invasive bladder cancer: an update.* Can Urol Assoc J, 2009. **3**(6 Suppl 4): p. S199-205.
15. Valstar, *Valstar (valrubicin) Sterile Solution for Intravesical Instillation*, in *ANTHRA PHARMACEUTICALS, INC.* 1998: Bedford, OH 44146 USA.
16. Gontero, P., et al., *The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin instillation therapy on the quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective, randomized, phase II trial.* J Urol, 2013. **190**(3): p. 857-62.
17. Abdallah, A.M., et al., *Complete genome sequence of Mycobacterium phlei type strain RIVM601174.* J Bacteriol, 2012. **194**(12): p. 3284-5.
18. Bergey, *Bergey's Manual of Determinative Bacteriology*. 9th ed.
19. Filion, M.C., et al., *Mycobacterium phlei cell wall complex directly induces apoptosis in human bladder cancer cells.* Br J Cancer, 1999. **79**(2): p. 229-35.
20. Killick, K.E., et al., *Receptor-mediated recognition of mycobacterial pathogens.* Cell Microbiol, 2013. **15**(9): p. 1484-95.

21. Filion, M.C., et al., *Modulation of interleukin-12 synthesis by DNA lacking the CpG motif and present in a mycobacterial cell wall complex.* Cancer Immunol Immunother, 2000. **49**(6): p. 325-34.
22. Redelman-Sidi, G., M.S. Glickman, and B.H. Bochner, *The mechanism of action of BCG therapy for bladder cancer--a current perspective.* Nat Rev Urol, 2014. **11**(3): p. 153-62.
23. D.R., C., *Regression Models and Life-Tables*. Journal of the Royal Statistical Society. Series B (Methodological). Vol. 34. 1972.
24. Schwalb, M.D., et al., *Positive urinary cytology following a complete response to intravesical bacillus Calmette-Guerin therapy: pattern of recurrence.* J Urol, 1994. **152**(2 Pt 1): p. 382-7.
25. Liedberg, F., *Early Complications and Morbidity of Radical Cystectomy.* EUROPEAN UROLOGY SUPPLEMENTS, 2010. **9**: p. 25-30.
26. Skinner, E.C., et al., *SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guerin.* J Urol, 2013. **190**(4): p. 1200-4.
27. Herr, H.W., T.N. Milan, and G. Dalbagni, *BCG-refractory vs. BCG-relapsing non-muscle-invasive bladder cancer: a prospective cohort outcomes study.* Urol Oncol, 2015. **33**(3): p. 108 e1-4.
28. Shirakawa, H., et al., *Prognostic significance of Bacillus Calmette-Guerin failure classification in non-muscle-invasive bladder cancer.* BJU Int, 2012. **110**(6 Pt B): p. E216-21.

Alternate Description for Figures 5 and 6

Page 31, Figure 5.
This graph is a swimmer's plot representing the outcomes for all 129 enrolled on Study 301 based on FDA analysis. The individual subjects by order of DFS duration are represented on the y-axis and the time in days along the x–axis. The time of cystectomy and occurrence of metastatic bladder cancer is also included, if known.

Page 34, Figure 6.
This graph is a swimmer's plot for the 93 subjects with baseline CIS-containing disease and highlights the 25 subjects that were in CR at 6 months. The individual subjects by order of DFS duration are represented on the y-axis and the time in days along the x–axis. The number of prior BCG instillations is indicated and whether the subjects were BCG-relapsing or BCG-refractory is noted. Finally, the time of cystectomy and occurrence of metastatic bladder cancer is also included, if known.